ON THE HYPERPLASIA OF NERVE CENTERS RESULTING FROM EXCESSIVE PERIPHERAL LOADING

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A number of investigators (Braus,[1] Shorey,[2] Dürken,[3] and Burr[4]) have shown that the destruction of peripheral areas in the embryo may result in an incomplete development (hypoplasia) of the nerve centers, either encephalic or spinal, which normally supply the peripheral area with nerves—the defective development resulting, supposedly, from a lack of functional demands which are ordinarily imposed upon the developing nerve centers. Particularly has this been observed in connection with experiments on the development of amphibian limbs.

The cumulative evidence favors the idea that *complete* development of the nerve centers will not take place unless under the influence of the functional activity of the end organ. The extent, however, to which function may effect development is a question concerning which the results of investigators stand at variance. Moreover, no experiments have hitherto been carried out to show whether, by increasing the functional demands at the periphery, it is possible to effect a corresponding increased development (hyperplasia) of the nerve centers.

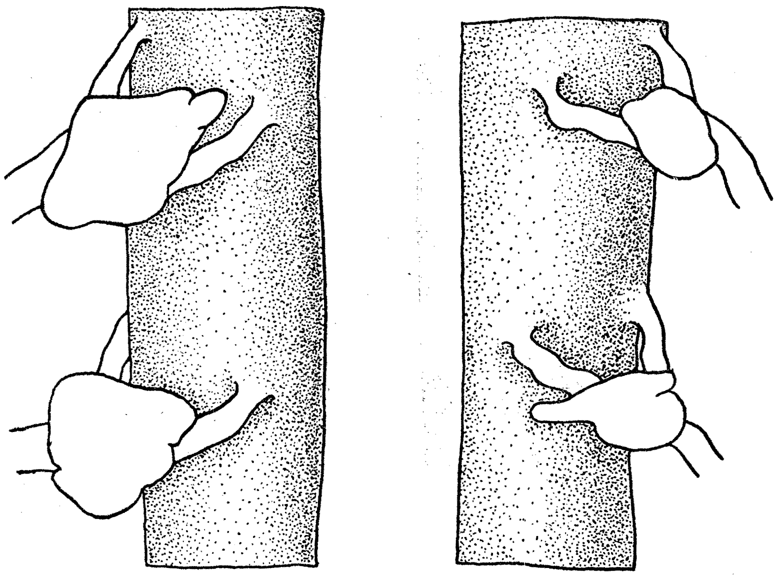
The experiments reported in this paper have shown that by effecting an increase in the peripheral area it was possible to bring about a hyperplasia of the sensory nerve centers. The experiments which have disclosed this fact consisted in transplanting the right anterior limb rudiment of Amblystoma punctatum a given number of body segments posterior to the normal position, whereby it was possible to study the effects of the continued function of limbs so placed upon the development of the sensory and motor nerve centers in that region of the cord supplying the limb with nerves. A brief account of the innervation and the function of limbs so transplanted has previously been published (Detwiler[5]).

Limbs transplanted the distance of more than three segments posterior to the normal position receive the bulk of their nerve supply from segments of the cord just posterior to the normal limb level. An examination of the peripheral nerves of this level shows that those contributing fibers to the functioning transplanted limbs are larger than their counterparts which are not connected with a limb.

In an endeavor to show whether this increase in the number of peripheral neurones was due to a hyperplasia of the motor centers, attempts were made to compare the number of motor nerve cell bodies in both halves of the spinal cord at the level in question. The larvae having been preserved at a relatively young stage (sixty to seventy days after the closure of the medullary folds), it was impossible to differentiate accurately be-

tween the nervous and non-nervous cells. Nevertheless, the results obtained from counting approximately eighty thousand cells, in addition to a comparative study of the size of the ventral roots, indicated that a hyperplasia of the motor centers had not taken place.

The evidence, however, of a hyperplasia of the sensory centers was very specific. In case $AS4_{26}$ the right anterior limb, which was transplanted the distance of four segments posterior to the normal limb level, was innervated by the fifth, sixth and seventh segments of the cord—the normal



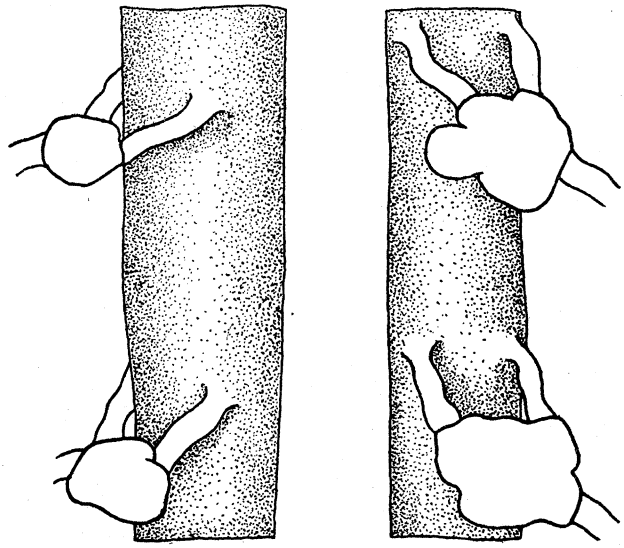
1 2

FIG. 1. Drawing of a reconstruction model showing the third and fourth left spinal ganglia (connected with the normal intact limb). × 50

FIG. 2. Drawing of a reconstruction model of the third and fourth spinal ganglia showing great reduction in size as a result of excision of the limb. × 50

intact left limb receiving its innervation from the third, fourth and fifth segments.[6] The right sixth and seventh spinal ganglia (connected with the transplanted limb) were found to be considerably larger than the corresponding ganglia on the left side (not connected with a limb), the comparative sizes being illustrated in figures 3 and 4. The results of counting the sensory nerve cells in the ganglia on the two sides showed clearly that the hypertrophy was due to a marked hyperplasia of the cells. The removal of the limb from its normal position, likewise, resulted in a marked reduction in the sizes of the third and fourth ganglia which normally supply it with sensory nerves (figs. 1 and 2).

By counting the cell bodies in the third and fourth ganglia on the left (those connected with the normal intact limb) and comparing with the number counted in the corresponding ganglia on the right side, where the peripheral area was greatly diminished as a result of the limb excision, a cell ratio between the normal and hypoplastic development was obtained. Further, by counting the number of cells in the sixth and seventh ganglia on the left (normal) side and comparing with the number found in the



3 4

FIG. 3. Drawing of a reconstruction model showing the sixth and seventh spinal ganglia which have no connection with a limb

FIG 4. Drawing of a reconstruction model showing hypertrophied sixth and seventh spinal ganglia supplying afferent innervation to a transplanted limb

right sixth and seventh ganglia, which contributed innervation to the transplanted limb, it was likewise possible to obtain a ratio between the normal and the hyperplastic development. A cell count was also made of the right and left ninth ganglia, which supplied homologous and undisturbed peripheral areas, as a control for the hypoplastic and hyperplastic cell estimates.

Having determined the cell ratios, the weight ratios were obtained by weighing and comparing the weights of unassembled paper models of the ganglia. The results of both computations (cell and weight) are summarized in the accompanying table. The extensive hypoplastic development of the right third and fourth ganglia resulting from the limb excision is readily seen, the total number of cells in each ganglion being less than

half the number present in the corresponding left ganglia with the limb intact. This is also emphasized by comparing the weights of the ganglia, the weight of the right third and fourth being less than half that of the corresponding left ganglia. The cell and weight ratios as seen in the table show an interesting approximation. The hyperplastic development of the right sixth and seventh ganglia connected with the transplanted limb is seen by comparing the number of cells in these structures with the number present in the corresponding left ganglia. A ratio closely approximating that of the cell count is shown by comparison of the weights.

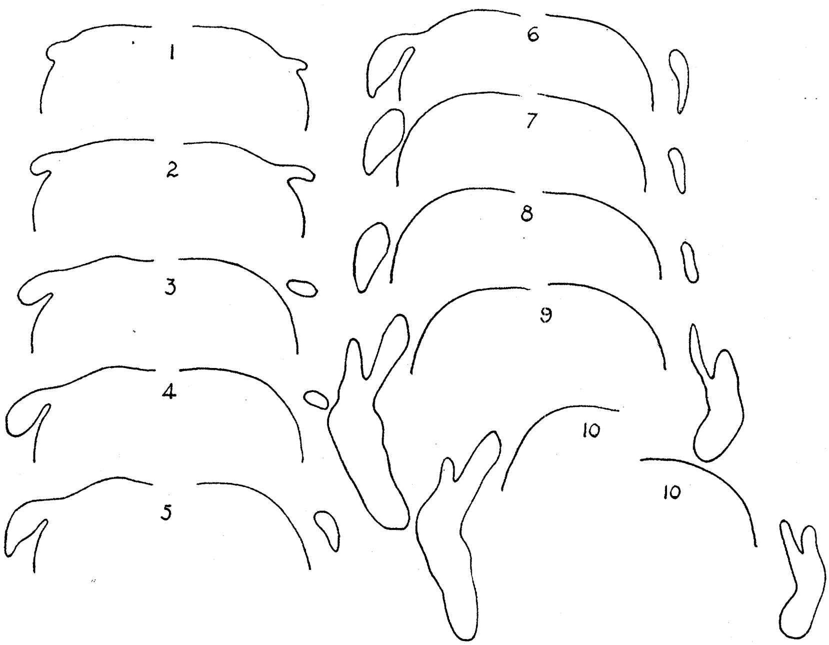


FIG. 5. Camera lucida drawing, showing serial sections of the sensory roots of the right and left third spinal nerve. The right root is greatly reduced in size as a result of excision of the right limb with which it is normally connected. × 40

Although a cell count of the fifth ganglia is included in the table, the results have no comparative value since both supply nerves to a limb. The cell content of the right ganglion connected with the transplanted limb is seen to be slightly greater than that of the left ganglion connected with the normal intact limb. The cell and weight ratios of the ninth ganglion which were used for a control show only an inappreciable difference which is well within the limit of error.

The number of cells in a given ganglion was estimated by counting the nuclei. The diameter of the nuclei in many cases being greater than the thickness of the section (10 μ), a considerable number of cells must have been counted twice. The percentage error being the same, however, in

all ganglia, regardless of size, a constant factor is introduced which has no appreciable effect on the cell ratios.

Hyperplasia of the sensory centers was also demonstrated by an increase in the size of the posterior (sensory) roots. The latter which were connected with the transplanted limb on the right side were found to be considerably larger than those on the left side, not connected with a limb

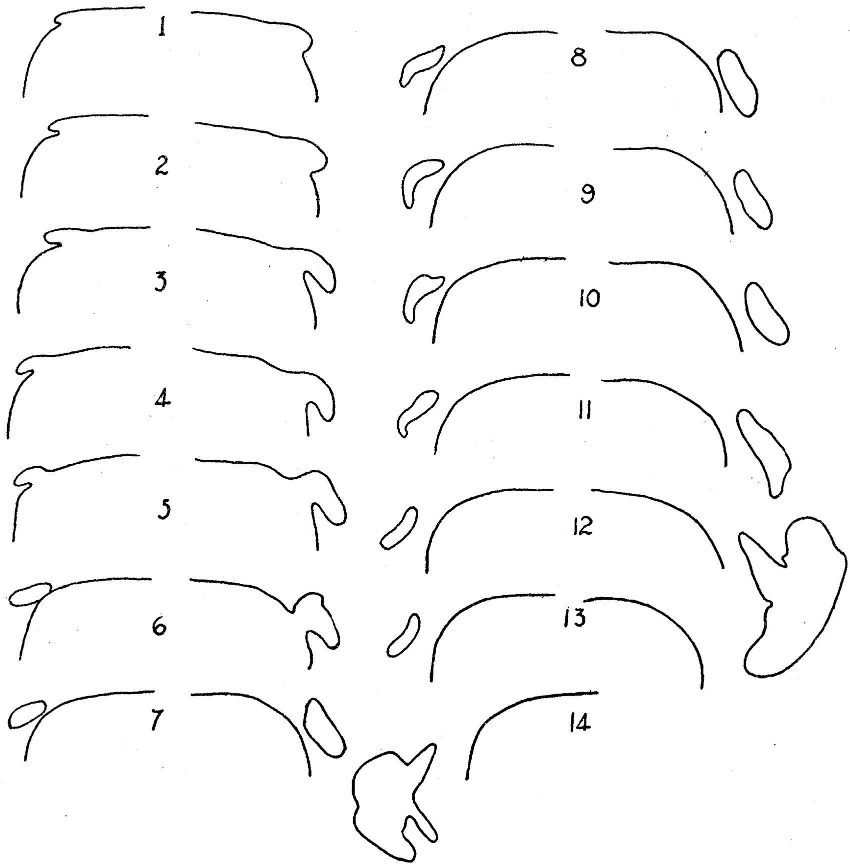


FIG. 6. Camera lucida drawing, showing serial sections of the sensory roots of the right and left seventh spinal nerve. The right root being connected with the transplanted limb is considerably larger than the left, which has no connection with a limb. × 40

(fig. 6). The hypoplasia of the sensory centers resulting from extirpating the limb was likewise shown by a great reduction in the size of the sensory roots, normally connected with the limb (fig. 5).

The results reported in this paper, as well as confirmatory evidence obtained from the study of other cases not reported ($AS5_{25}$, $AS5_{26}$, $AS5_{27}$, $AS5_{30}$), clearly show that excessive peripheral loading with a subsequent increase in the functional demands will result in a corresponding hyper-

plasia of the sensory nerve centers. Results so far accumulated suggest the possibility that motor regulation is accomplished by division of the peripheral axones. It is hoped that further experimentation will disclose a number of additional facts concerning the effect of peripheral overloading on the development of nerve centers.

SHOWING THE EFFECTS OF REMOVAL OF THE LIMB AND THE FUNCTUAL ACTIVITY OF THE TRANSPLANTED LIMB UPON THE DEVELOPMENT OF PERIPHERAL AFFERENT NEURONES

GANGLION CONNECTED WITH NORMAL INTACT LEFT LIMB			GANGLION WITH RIGHT LIMB REMOVED			GANGLION CONNECTED WITH RIGHT LIMB TRANSPLANTED TO A HETEROTOPIC POSITION			GANGLION NOT CONNECTED WITH EITHER LIMB			RATIOS	
No. of spinal ganglion	No. of cells counted	Weight of the model in grams	No. of spinal ganglion	No. of cells counted	Weight of the model in grams	No. of spinal ganglion	No. of cells counted	Weight of the model in grams	No. of spinal ganglion	No. of cells counted	Weight of the model in grams	Cell No.	Weight
3	1725	30.4841	3	850	12.9748							0.492	0.425
4	1430	26.1604	4	685	9.7311							0.479	0.372
5	955	16.8798				5	1195	22.2939				1.25	1.32
						6	1171	26.5422	6	693	12.6600	1.69	2.09
						7	1084	21.7634	7	720	11.7366	1.51	1.85
									9*	754	15.5456		
									9**	773	17.2328	1.02	1.10

* Left ganglion. ** Right ganglion.

[1] Braus, H., *Morph. Jahr.*, **35,** 1906.

[2] Shorey, M. L., *J. Exper. Zoöl.*, **17,** 1909.

[3] Dürken, B., *Zs. wiss. Zoöl.*, **99,** 1911.

[4] Burr, H. S., *J. Exper. Zoöl.*, **20,** 1916.

[5] Detwiler, S. R., these PROCEEDINGS, **5,** 1919.

[6] The innervation to the normal and the transplanted limb in Case $AS4_{26}$ is figured in the paper referred to above.